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Optimal Choice of Beta Blockers and ARBs for AMI Patients

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  - Korean Society of Interventional Cardiology
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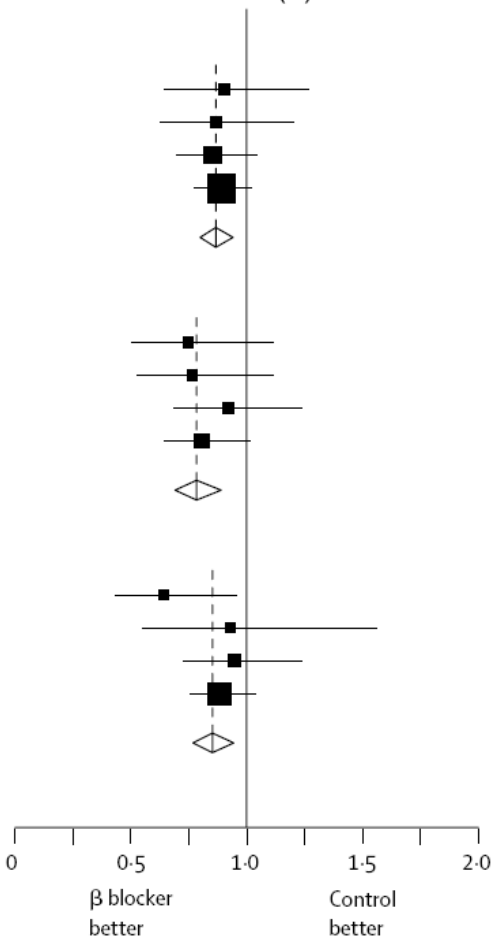
ACC/AHA guidelines 2013

- **Class I**
  1. Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: signs of HF, evidence of a low output state, increased risk for cardiogenic shock,‖ or other contraindications to use of oral beta blockers (PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease). (*Level of Evidence: B)*
  2. Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. (*Level of Evidence: B)*
  3. Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility. (*Level of Evidence: C)*

Meta-analysis of effects of intravenous then oral-blocker therapy

Category and trial	Events/patients (%) β blocker	Events/patients (%) Control	Proportional reduction
Death (any cause)			
26 small trials[15]	117/2901 (4·0%)	126/2830 (4·5%)	
MIAMI[7]	123/2877 (4·3%)	142/2901 (4·9%)	
ISIS-1[15]	317/8037 (3·9%)	367/7990 (4·6%)	
COMMIT (low-risk only)	708/12 374 (5·7%)	801/12 555 (6·4%)	
Total	1265/26 189 (4·8%)	1436/26 276 (5·5%)	13% (SE 4) (p=0·0006)
Reinfarction			
21 small trials[15]	75/2341 (3·2%)	99/2331 (4·2%)	
MIAMI[7]	85/2877 (3·0%)	111/2901 (3·8%)	
ISIS-1[15]	148/5807 (2·5%)	161/5834 (2·8%)	
COMMIT (low-risk only)	236/12 374 (1·9%)	295/12 555 (2·3%)	
Total	544/23 399 (2·3%)	666/23 621 (2·8%)	22% (SE 6) (p=0·0002)
Ventricular fibrillation or other cardiac arrest			
25 small trials[15]	69/2862 (2·4%)	105/2815 (3·7%)	
MIAMI[7]	48/2877 (1·7%)	52/2901 (1·8%)	
ISIS-1[15]	189/8037 (2·4%)	198/7990 (2·5%)	
COMMIT (low-risk only)	513/12 374 (4·1%)	586/12 555 (4·7%)	
Total	819/26 150 (3·1%)	941/26 261 (3·6%)	15% (SE 5) (p=0·002)

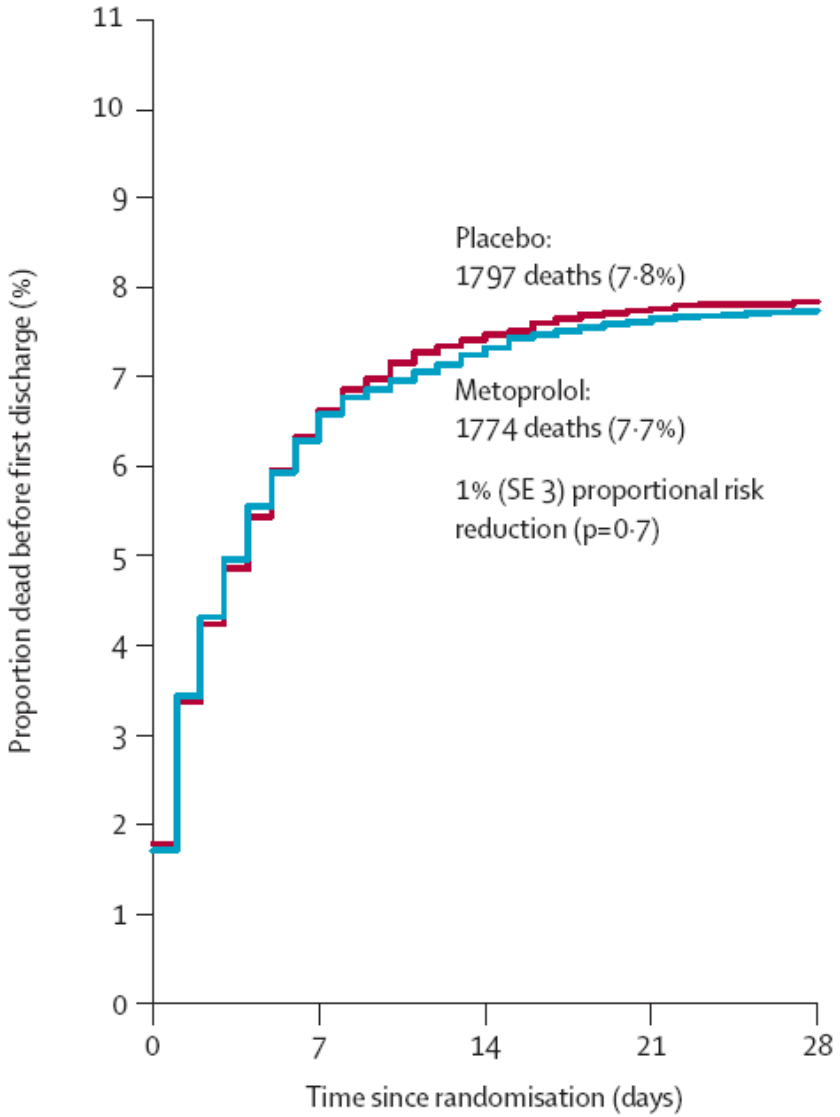


Chen ZM et al. *Lancet* 2005; 366: 1622–32

COMMIT trial

Effects of metoprolol allocation on death before first discharge from hospital

Patients scheduled for primary PCI were to be excluded.



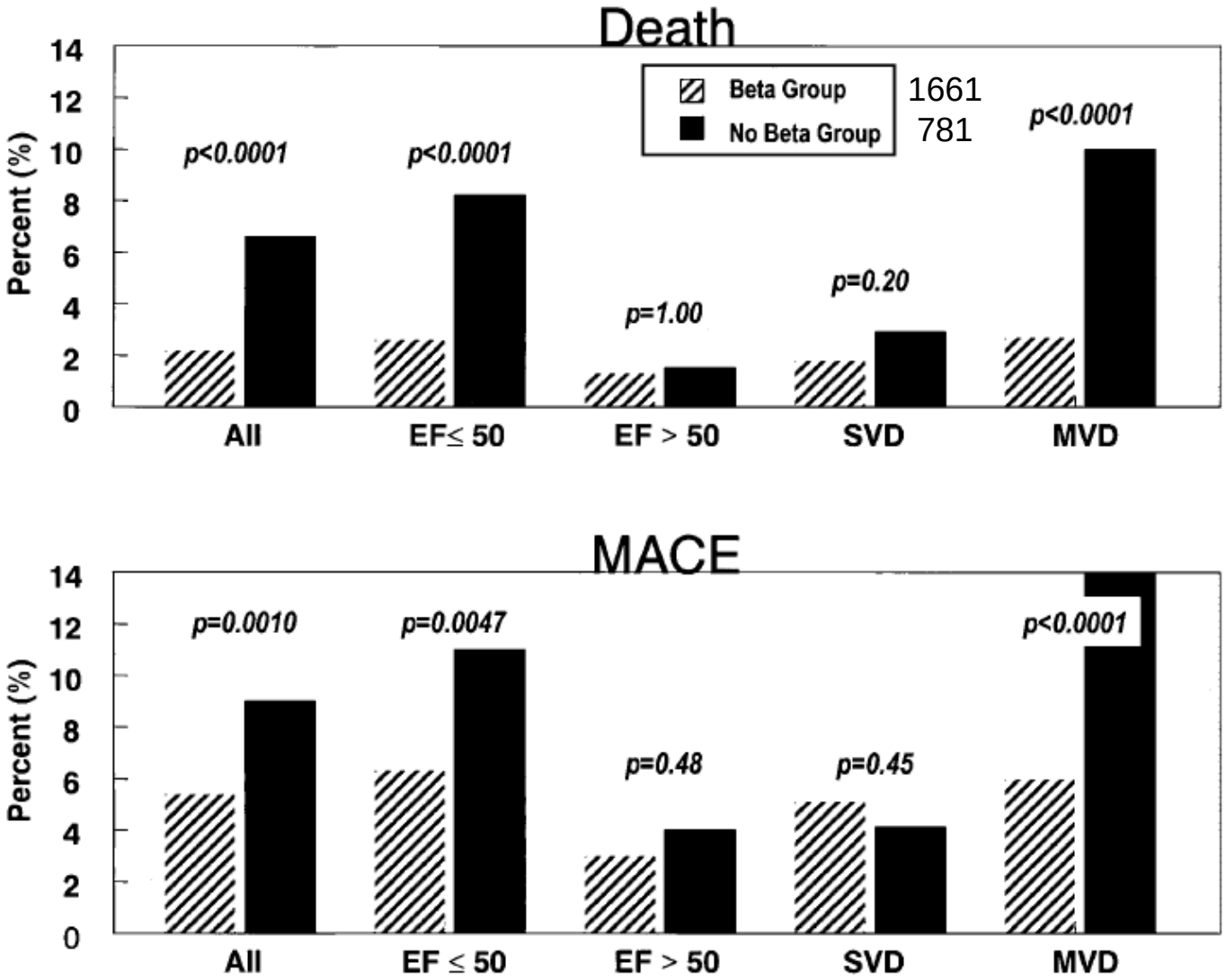
Days	0–6	7–13	14–20	21–28
Number of events				
Metoprolol	1441	220	83	30
Placebo	1449	249	75	24

Chen ZM et al. *Lancet* 2005; 366: 1622–32

In patients undergoing primary PCI

- No randomized trial of beta-blocker therapy in patients with STEMI undergoing PCI without fibrinolytic therapy has been performed.

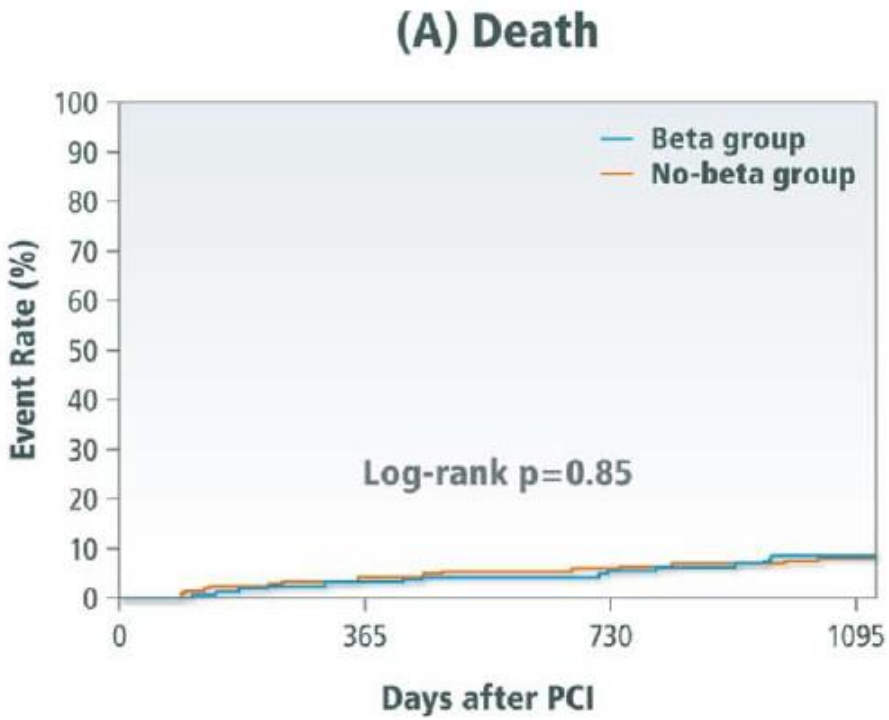
Beta blocker is needed.

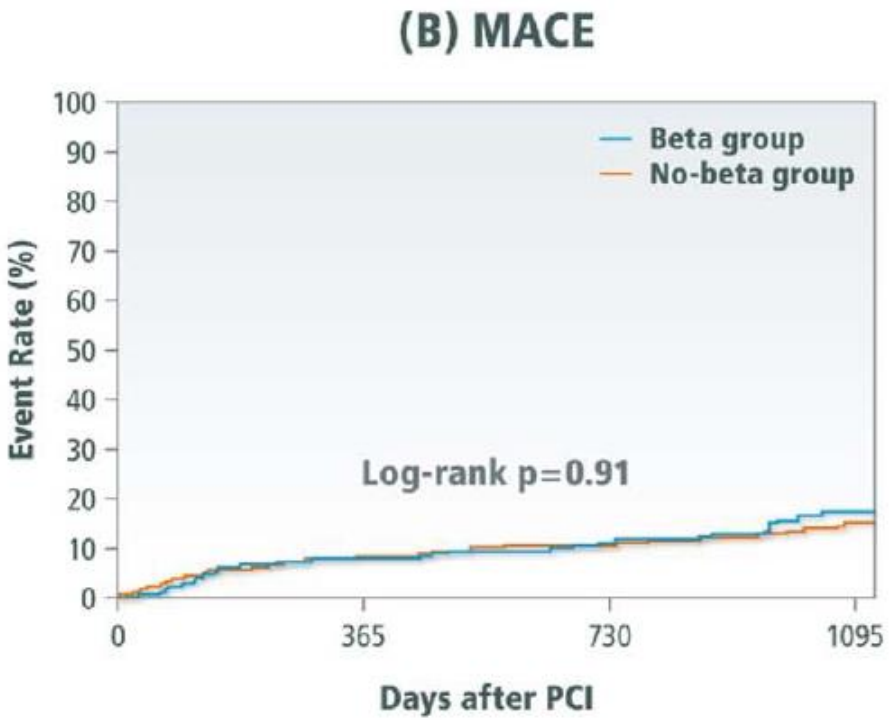


J Am Coll Cardiol 2004;43:1773–9

Beta blocker is not beneficial.

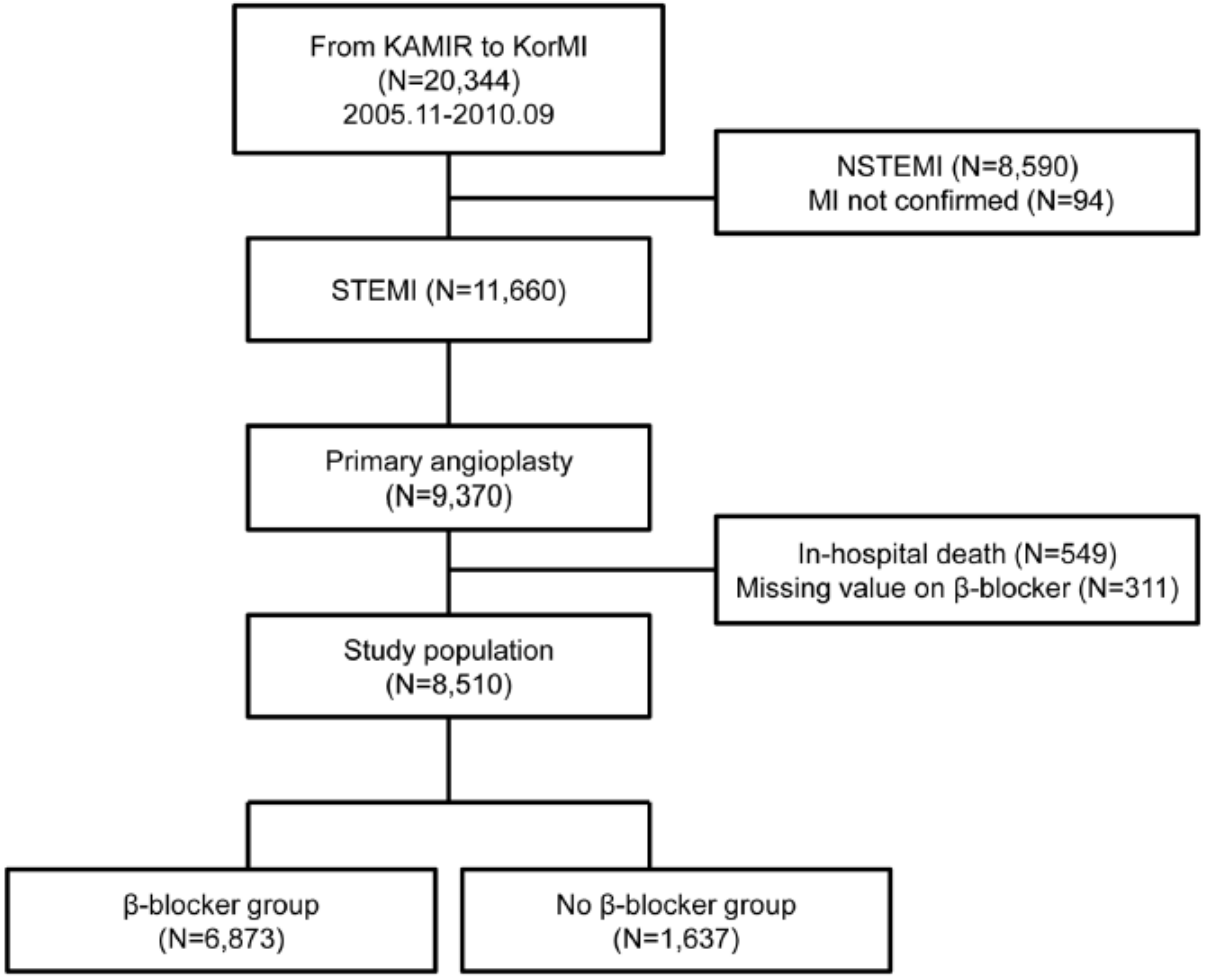
J-Cypher registry
Beta group = 349
No-beta group = 561





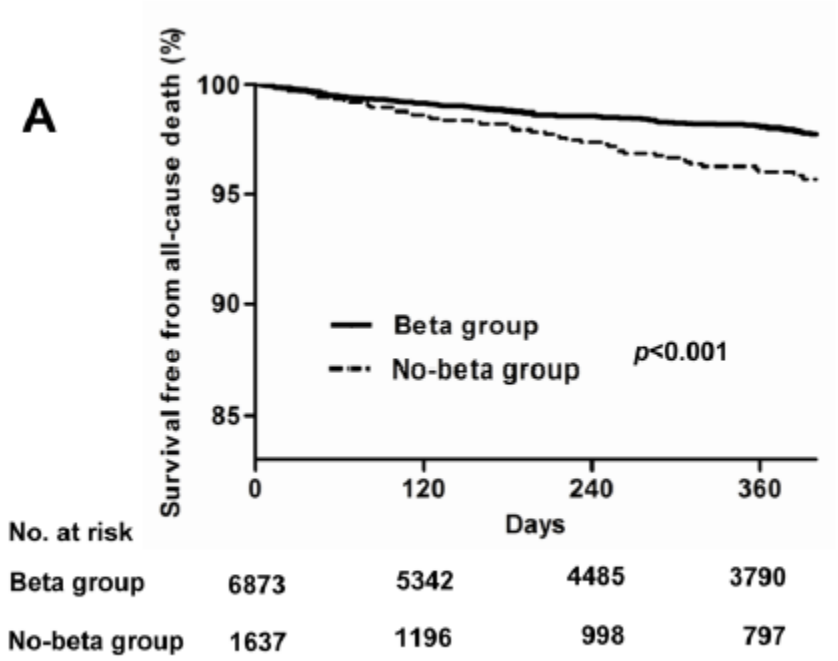
Am J Cardiol 2010;106:1225–1233

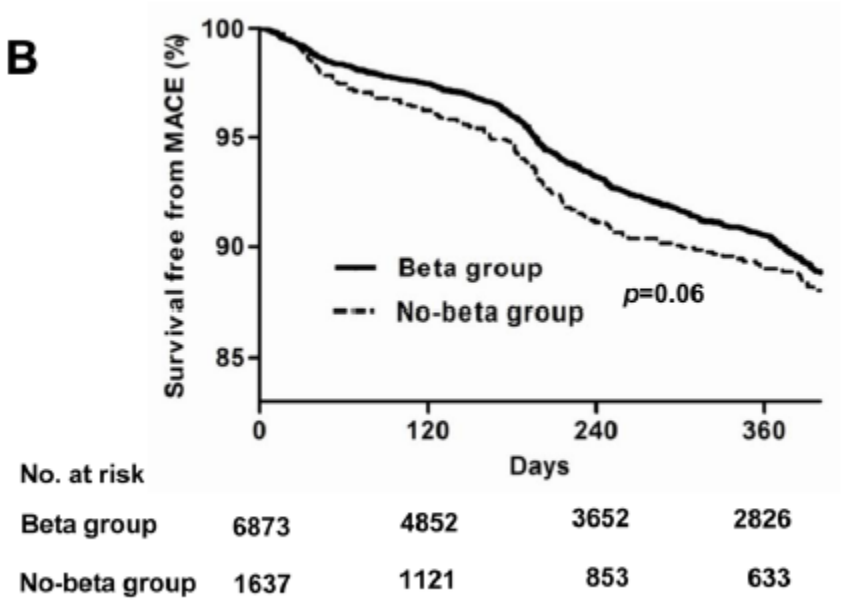
Study Population



Yang JH, Hahn JY et al. J Am Coll Cardiol Intv 2014;7:592–601

In overall patients





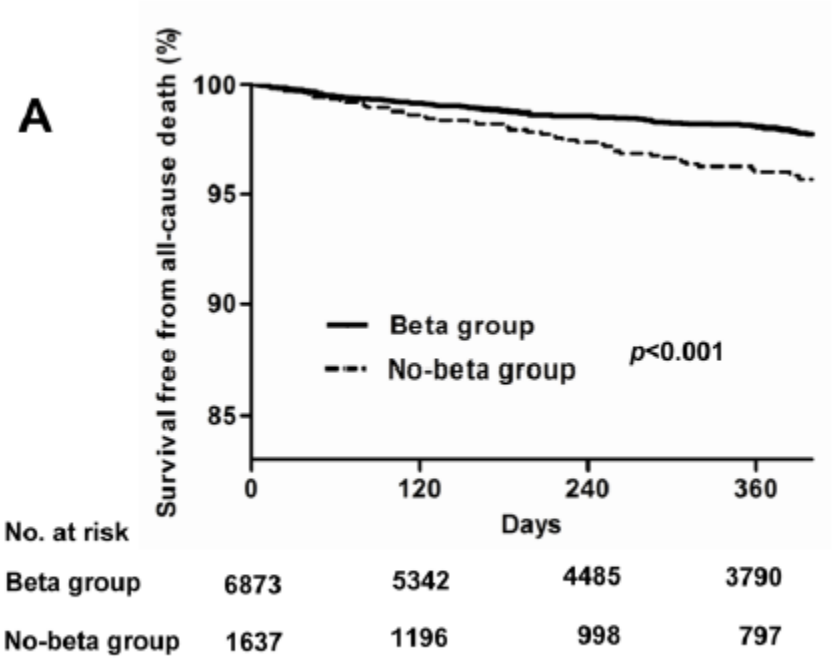
J Am Coll Cardiol Intv 2014;7:592–601

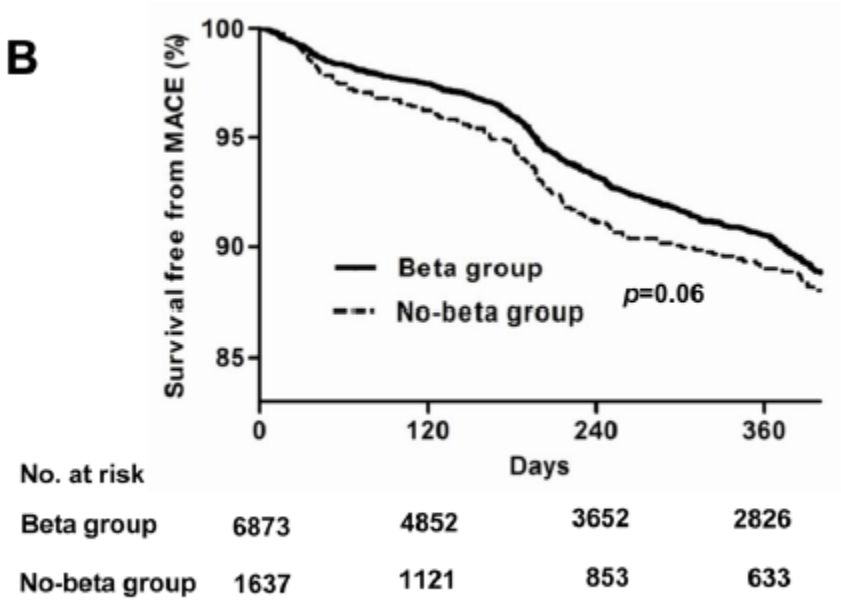
Clinical Outcomes in Propensity-matched Population

Propensity-Matched Population (n=3,975)	β-Blocker Group (n=2650)	No-β-Blocker Group (n=1325)	Adjusted HR* (95% CI)	*p* value
All-cause death	74 (2.8)	54 (4.1)	0.46 (0.27-0.78)	0.004
Cardiac death	40 (1.5)	37 (2.8)	0.39 (0.19-0.79)	0.01
Myocardial infarction	30 (1.1)	19 (1.4)	0.61 (0.28-1.36)	0.23
All-cause death or MI	101 (3.8)	70 (5.3)	0.60 (0.40-0.91)	0.02
Any coronary revascularization	141 (5.3)	85 (6.4)	0.85 (0.59-1.22)	0.38
Major adverse cardiac events†	219 (8.3)	140 (10.6)	0.78 (0.59-1.02)	0.07

J Am Coll Cardiol Intv 2014;7:592–601

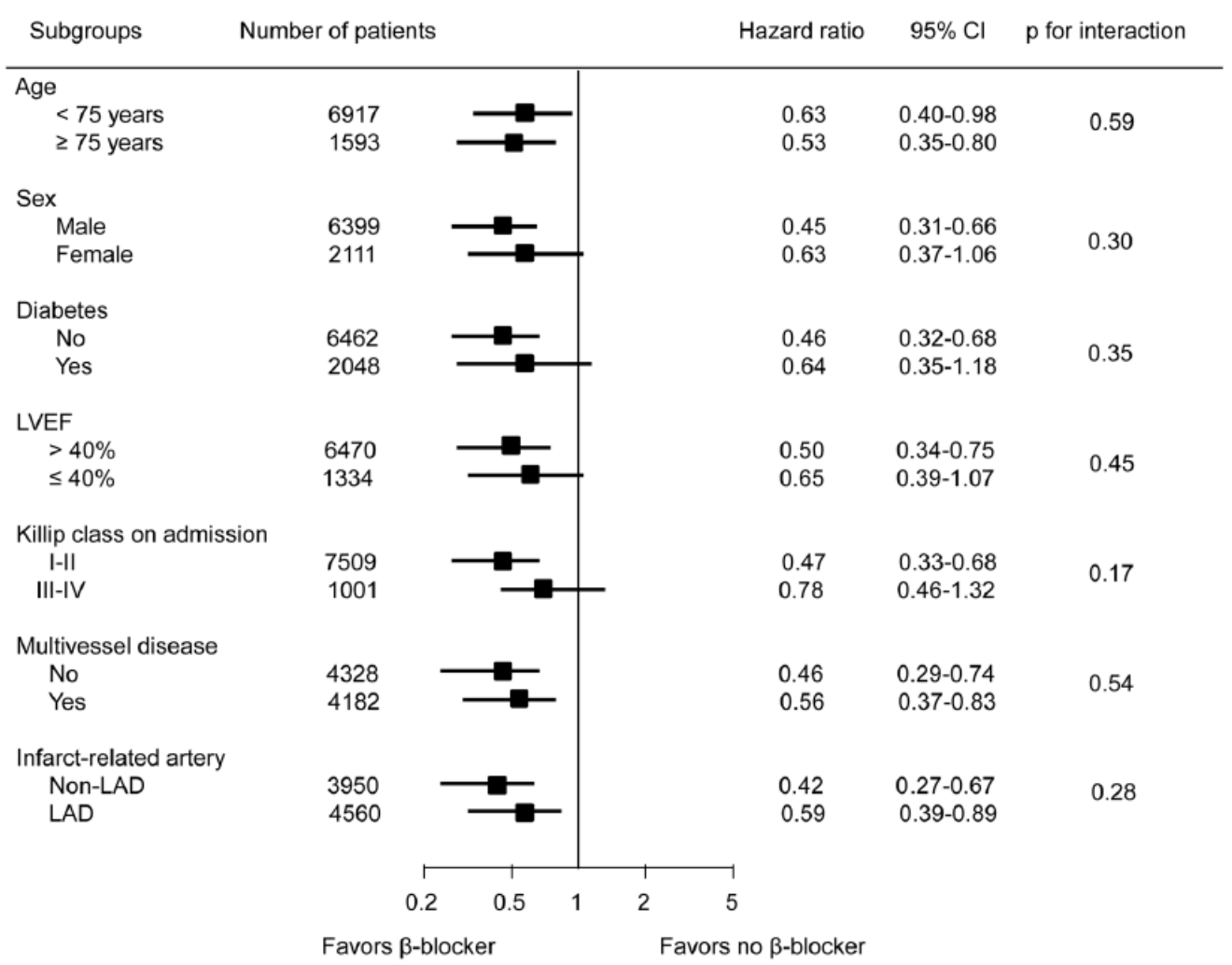
In propensity-matched populations





J Am Coll Cardiol Intv 2014;7:592–601

Subgroup analysis



J Am Coll Cardiol Intv 2014;7:592–601

Summary

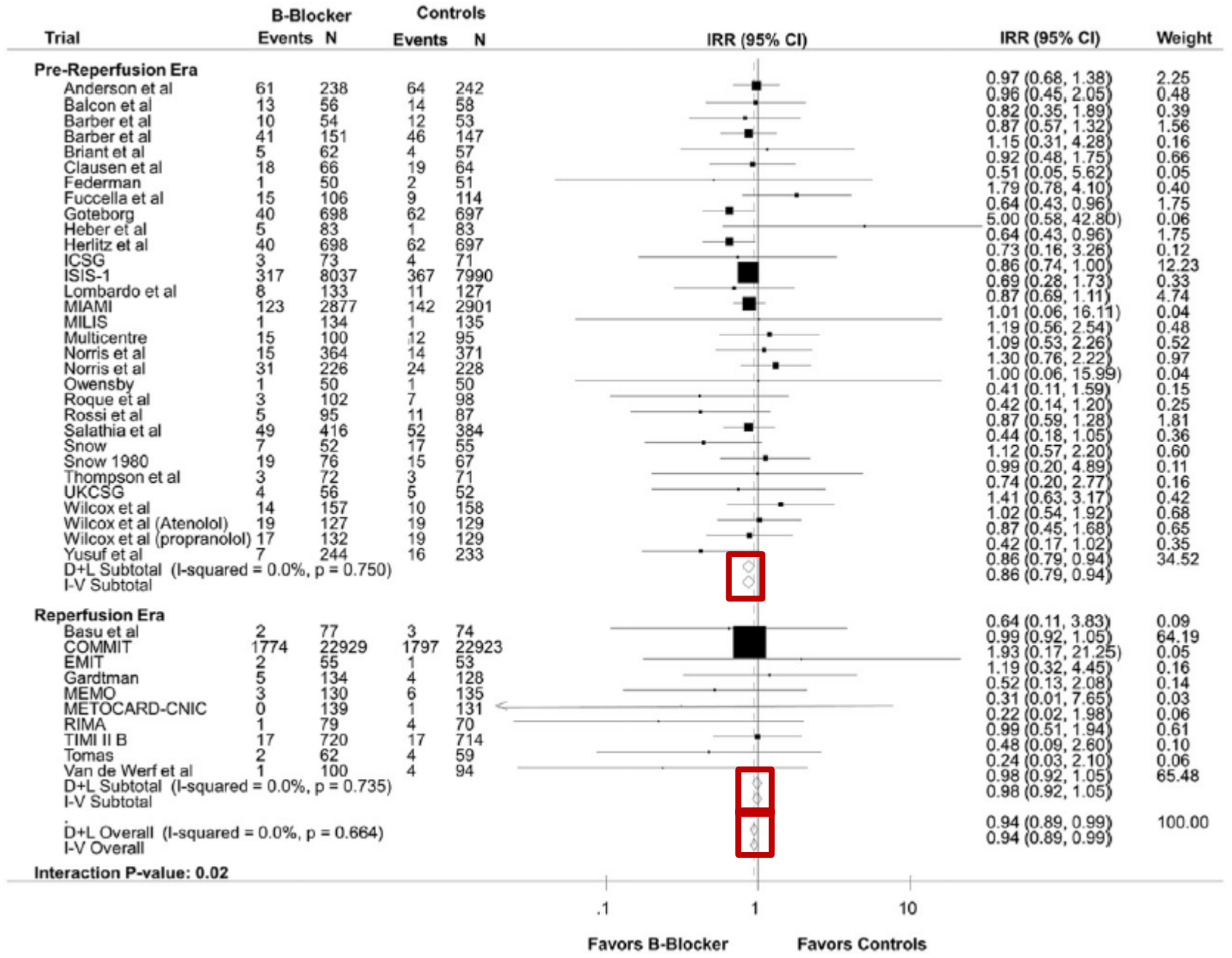
- β-blocker therapy at discharge was associated with lower mortality.
- This result was maintained in propensity-matched populations.
- Furthermore, the association with better outcome of β-blocker therapy in terms of all-cause death was consistent across various subgroups.

Drugs and Dose

Indications	Dose/Administration
• Oral: All patients without contraindication • IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Individualize: • Metoprolol tartrate 25 to 50 mg every 6 to 12 h orally, then transition over next 2 to 3 d to twice-daily dosing of metoprolol tartrate or to daily metoprolol succinate; titrate to daily dose of 200 mg as tolerated • Carvedilol 6.25 mg twice daily, titrate to 25 mg twice daily as tolerated • Metoprolol tartrate IV 5 mg every 5 min as tolerated up to 3 doses; titrate to heart rate and BP

Avoid/Caution

Signs of HF, Low output state, Increased risk of cardiogenic shock, Prolonged first-degree or high-grade AV block, Reactive airways disease



Am J Med. 2014 Oct;127(10):939-53.

Landmark analysis

Table 2 Landmark Analyses: β-Blockers vs Controls (From Fixed-effect Model)

	Death	CV Death	Sudden Death	MI	Heart Failure
Events at 30 days					
Pre-reperfusion	0.87 (0.79, 0.96)	0.86 (0.77, 0.96)	0.82 (0.59, 1.13)	0.81 (0.63,1.04)	1.06 (0.97, 1.16)
Reperfusion era	0.98 (0.92, 1.05)	1.00 (0.91,1.10)	0.94 (0.86, 1.01)	0.72 (0.62, 0.84)	1.10 (1.05, 1.16)
Events between 30 days and 1 year					
Pre-reperfusion	0.79 (0.71, 0.88)	0.84 (0.71, 1.00)	0.61 (0.49, 0.76)	0.77 (0.64, 0.91)	1.07 (0.91, 1.27)
Reperfusion era	1.50 (0.53, 4.21)	1.50 (0.53, 4.21)	NA	0.71 (0.23, 2.25)	3.83 (1.56, 9.41)
Events > 1 year					
Pre-reperfusion	0.81 (0.66, 0.98)	0.73 (0.48, 1.11)	0.64 (0.43, 0.97)	0.81 (0.62, 1.06)	0.25 (0.03, 2.25)
Reperfusion era	NA	NA	NA	NA	NA

Conclusions

- In the primary PCI era, no randomized trial of beta-blocker therapy in patients with STEMI has been performed.
- The role of beta blockers in patients with STEMI undergoing primary PCI remains controversial.
  - Beneficial or useless or harmful?
  - Which drug?
  - How long?
- Future studies are needed.

ACC/AHA STEMI guideline 2013

- Class I
  1. An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) less than or equal to 0.40, unless contraindicated.[420–423] (Level of Evidence: A)
  2. An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors.[424,425] (*Level of Evidence: B*)

- Class IIa
  1. ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use.[427–429] (*Level of Evidence: A*)

ESC STEMI guidelines 2012

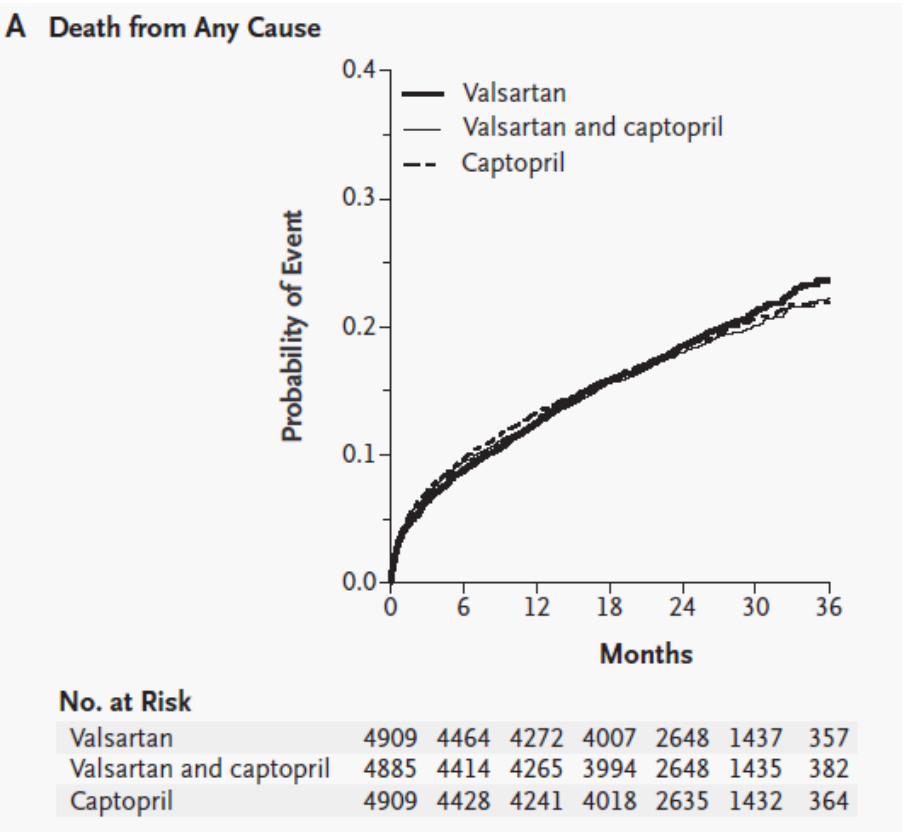
- Class I
  - ACE inhibitors are indicated starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. (Level of Evidence: A)
  - An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. (Level of Evidence: B)

- Class IIa
  - ACE inhibitors should be considered in all patients in the absence of contraindications. (Level of Evidence: A)

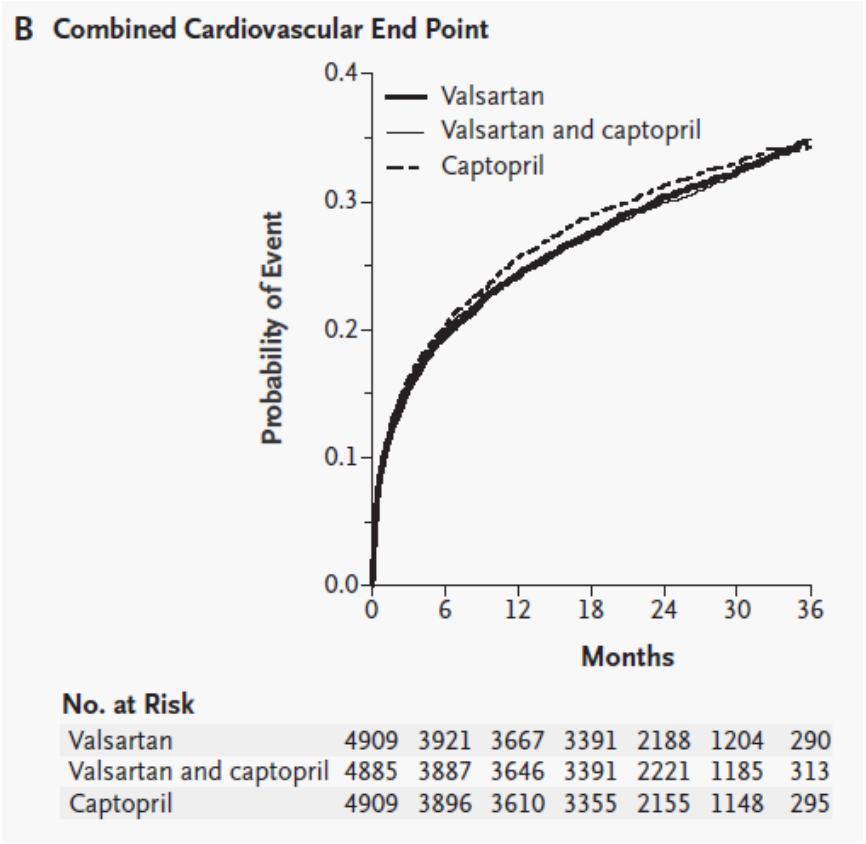
ARBs in patients with AMI

VALIANT trial

AMI patients with CHF or LV systolic dysfunction



No. at Risk							
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan and captopril	4885	4414	4265	3994	2648	1435	382
Captopril	4909	4428	4241	4018	2635	1432	364



No. at Risk							
Valsartan	4909	3921	3667	3391	2188	1204	290
Valsartan and captopril	4885	3887	3646	3391	2221	1185	313
Captopril	4909	3896	3610	3355	2155	1148	295

N Engl J Med 2003;349:1893-906

Treatment for STEMI in Korea

- One-year mortality
  - 6.7% for primary PCI from the Korean AMI registry
    - Song YB, Hahn JY, Gwon HC et al. Am J Cardiol 2010;106:1397-403.
- Primary PCI
  - The overwhelmingly preferred reperfusion strategy
  - Performed in 85% of reperfusion eligible patients with STEMI
    - Song YB, Hahn JY, Gwon HC et al. J Korean Med Sci 2008; 23: 431-8.
- LV systolic function is preserved in most patients.
    - Yang JH, Hahn JY et al. J Am Coll Cardiol Intv 2014
- Cough developed commonly after ACE inhibor use.
  - Upto 40%.
    - Na SH et al. Korean Circulation J 2000;30:1540-1545.

ACC/AHA STEMI guideline 2013

- Class I
  1. An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) less than or equal to 0.40, unless contraindicated.[420–423] (Level of Evidence: A)
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BMJ 2014;349:g6650 doi: 10.1136/bmj.g6650 (Published 14 November 2014)

RESEARCH

Angiotensin receptor blocker in patients with ST segment elevation myocardial infarction with preserved left ventricular systolic function: prospective cohort study

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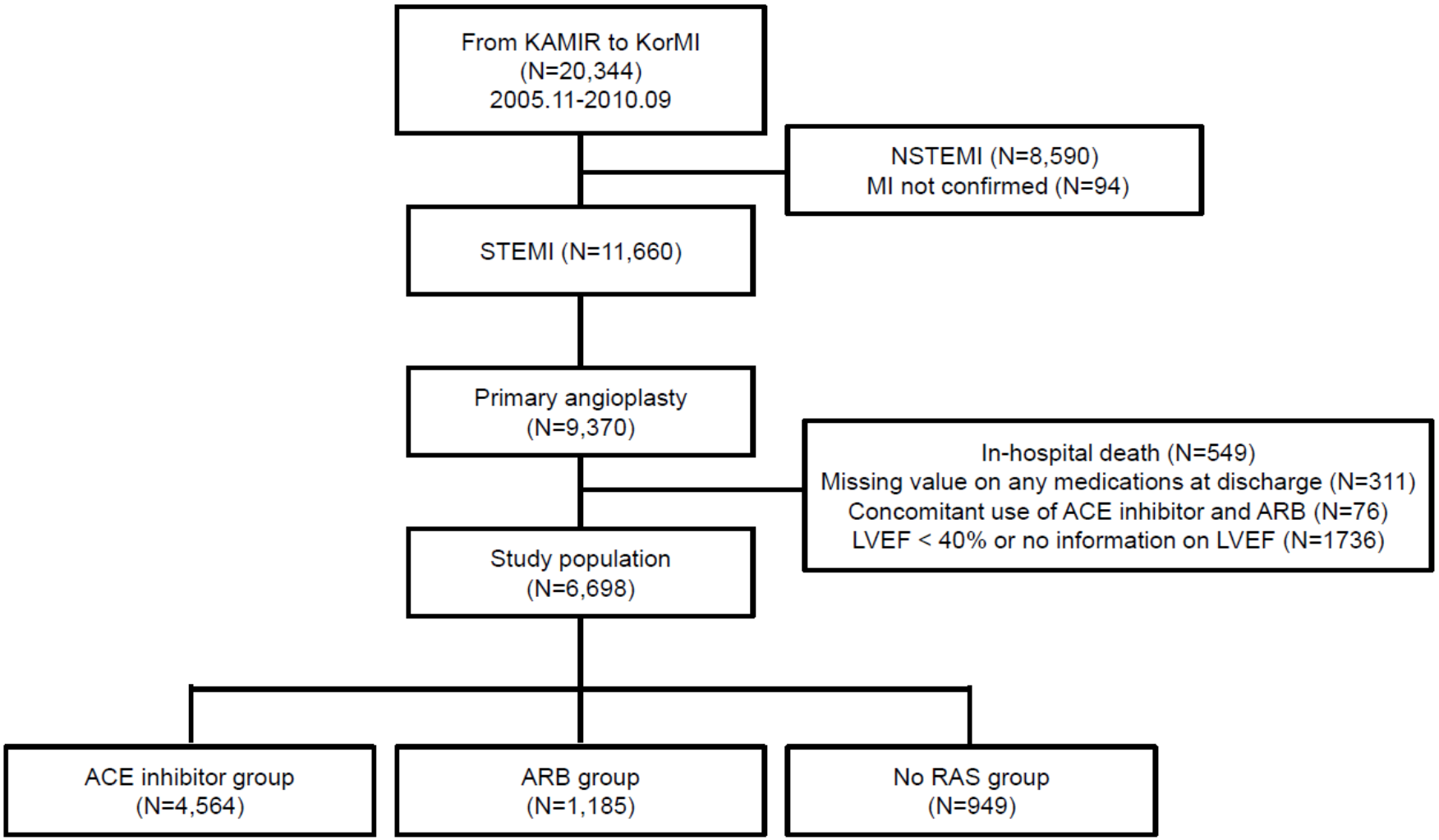
Study Population



Clinical Outcomes

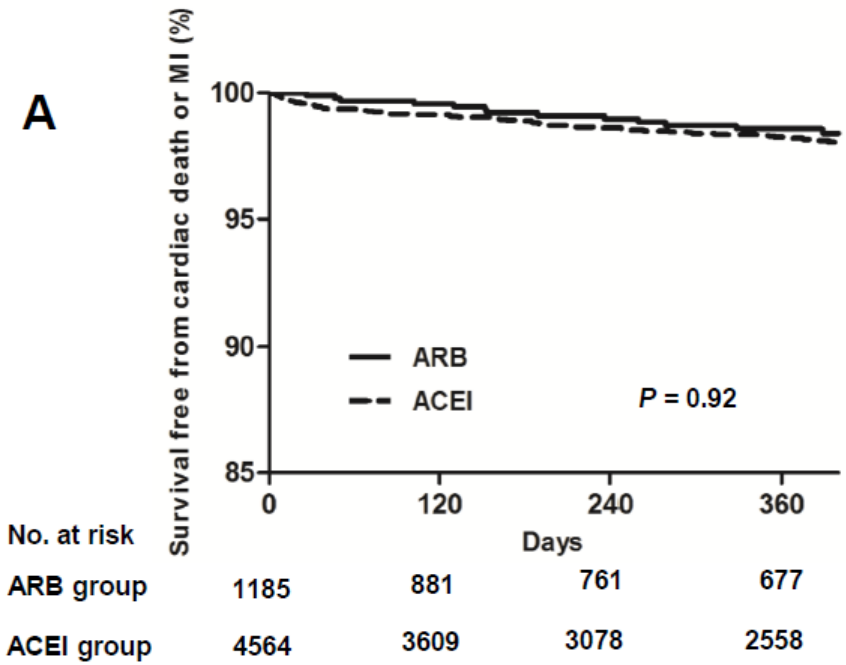
Total Population (n=5,749)	ARB (n=1,185)	ACEI (n=4,564)	Unadjusted HR (95% CI)	*P* value	Adjusted HR[a] (95% CI)	*P* value
Cardiac death or MI	21 (1.8)	77 (1.7)	1.02 (0.63-1.66)	0.92	0.94 (0.58-1.53)	0.79
All-cause death	32 (2.7)	64 (1.4)	1.85 (1.21-2.83)	0.01	1.54 (1.00-2.37)	0.05
Cardiac death	15 (1.3)	35 (0.8)	1.61 (0.88-2.96)	0.12	1.33 (0.72-2.46)	0.36
Myocardial infarction	7 (0.6)	43 (0.9)	0.61 (0.27-1.35)	0.22	0.59 (0.26-1.31)	0.19
Total Population (n=2,134)	ARB (n=1,185)	No RAS (n=949)	Unadjusted HR (95% CI)	*P* value	Adjusted HR[b] (95% CI)	*P* value
Cardiac death or MI	21 (1.8)	33 (3.5)	0.44 (0.25-0.76)	0.004	0.49 (0.27-0.87)	0.02
All-cause death	32 (2.7)	29 (3.1)	0.74 (0.45-1.23)	0.25	0.82 (0.48-1.40)	0.47
Cardiac death	15 (1.3)	18 (1.9)	0.57 (0.29-1.13)	0.11	0.69 (0.33-1.44)	0.32
Myocardial infarction	7 (0.6)	15 (1.6)	0.33 (0.13-0.81)	0.02	0.29 (0.11-0.76)	0.01

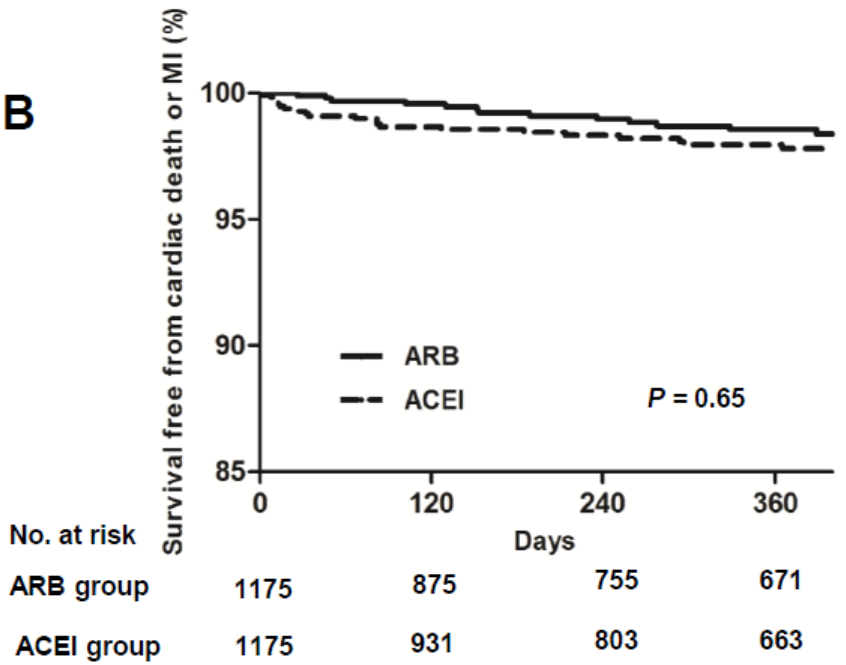
Propensity score matched analysis

Table 4| **Clinical outcomes in patients with ST segment elevation myocardial infarction with preserved left ventricular systolic according to treatment at discharge and during follow-up in propensity matched population. Figures are numbers (percentage) of patients and hazard ratios (95% confidence interval)**

Propensity matched population	Angiotensin receptor blocker	Comparison group	Adjusted* HR (95% CI)	P value
Comparison with ACE inhibitor (n=1175 in each group				
Cardiac death or MI	21 (1.8)	23 (2.0)	0.65 (0.30 to 1.38)	0.65
All cause death	32 (2.7)	18 (1.5)	1.23 (0.59 to 2.56)	0.58
Cardiac death	15 (1.3)	11 (0.9)	1.14 (0.41 to 3.15)	0.80
Myocardial infarction	7 (0.6)	12 (1.0)	0.30 (0.08 to 1.09)	0.07
Comparison with no renin angiotensin system blocker (n=803 in each group)				
Cardiac death or MI	14 (1.7)	25 (3.1)	0.35 (0.14 to 0.90)	0.03
All cause death	21 (2.6)	23 (2.9)	0.81 (0.36 to 1.85)	0.62
Cardiac death	10 (1.2)	13 (1.6)	0.47 (0.14 to 1.56)	0.22
Myocardial infarction	4 (0.5)	12 (1.5)	0.25 (0.05 to 1.18)	0.08

ARB versus ACEi

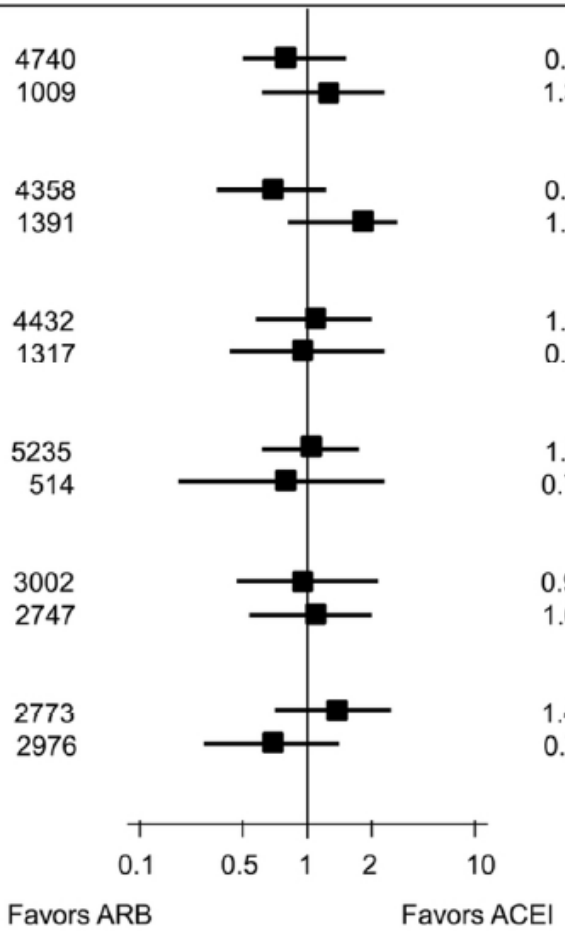




Yang JH, Hahn JY, submitted

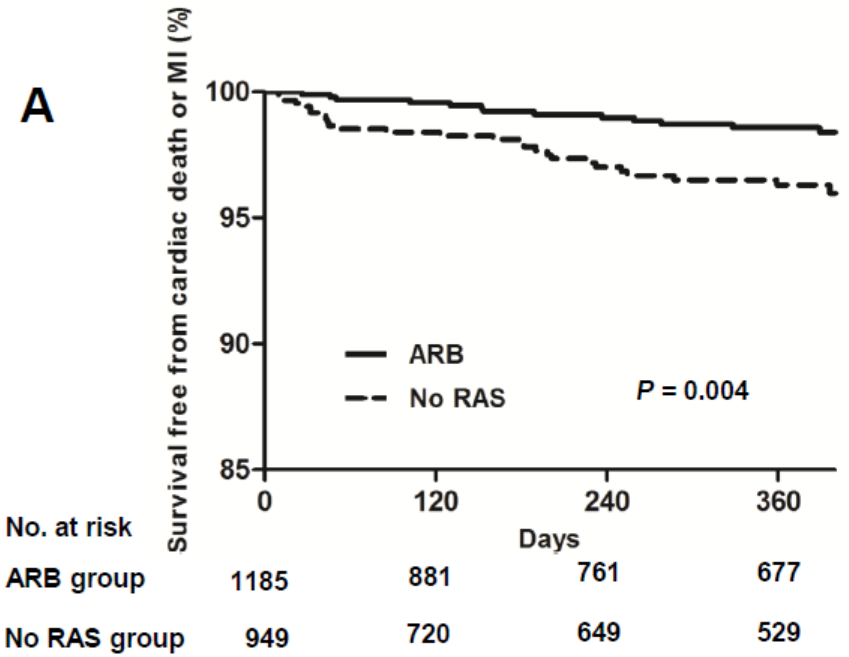
ARB versus ACEi

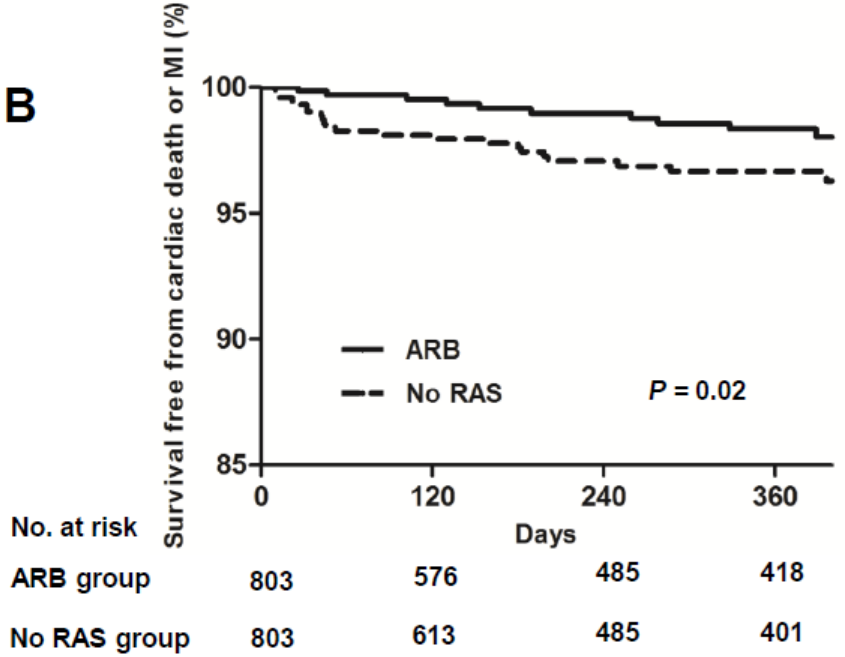
Subgroups	Number of patients	Hazard ratio	95% CI	P for interaction
Age				
< 75 years	4740	0.84	0.45-1.57	0.31
≥ 75 years	1009	1.33	0.61-2.91	
Sex				
Male	4358	0.70	0.36-1.37	0.05
Female	1391	1.82	0.87-3.81	
Diabetes				
No	4432	1.10	0.62-1.95	0.74
Yes	1317	0.95	0.39-2.32	
Killip class on admission				
I-II	5235	1.04	0.61-1.79	0.68
III-IV	514	0.78	0.26-2.35	
Multivessel disease				
No	3002	0.94	0.43-2.04	0.75
Yes	2747	1.07	0.58-1.99	
Infarct-related artery				
Non-LAD	2773	1.47	0.75-2.89	0.13
LAD	2976	0.71	0.35-1.46	



Yang JH, Hahn JY, submitted

ARB versus no RAS blockers

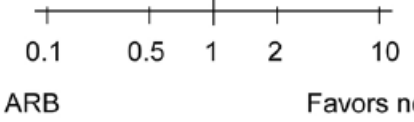




Yang JH, Hahn JY, submitted

ARB versus no RAS blockers

Subgroups	Number of patients	Hazard ratio	95% CI	P for interaction
Age				
< 75 years	1707	0.34	0.16-0.70	0.33
≥ 75 years	427	0.60	0.25-1.46	
Sex				
Male	1566	0.32	0.14-0.70	0.35
Female	568	0.57	0.26-1.25	
Diabetes				
No	1635	0.42	0.22-0.80	0.58
Yes	499	0.55	0.19-1.58	
Killip class on admission				
I-II	1900	0.46	0.25-0.86	0.91
III-IV	234	0.41	0.12-1.39	
Multivessel disease				
No	1106	0.23	0.10-0.55	0.08
Yes	1028	0.71	0.33-1.54	
Infarct-related artery				
Non-LAD	1059	0.51	0.24-1.09	0.47
LAD	1075	0.33	0.15-0.76	



Yang JH, Hahn JY, submitted

Limitations

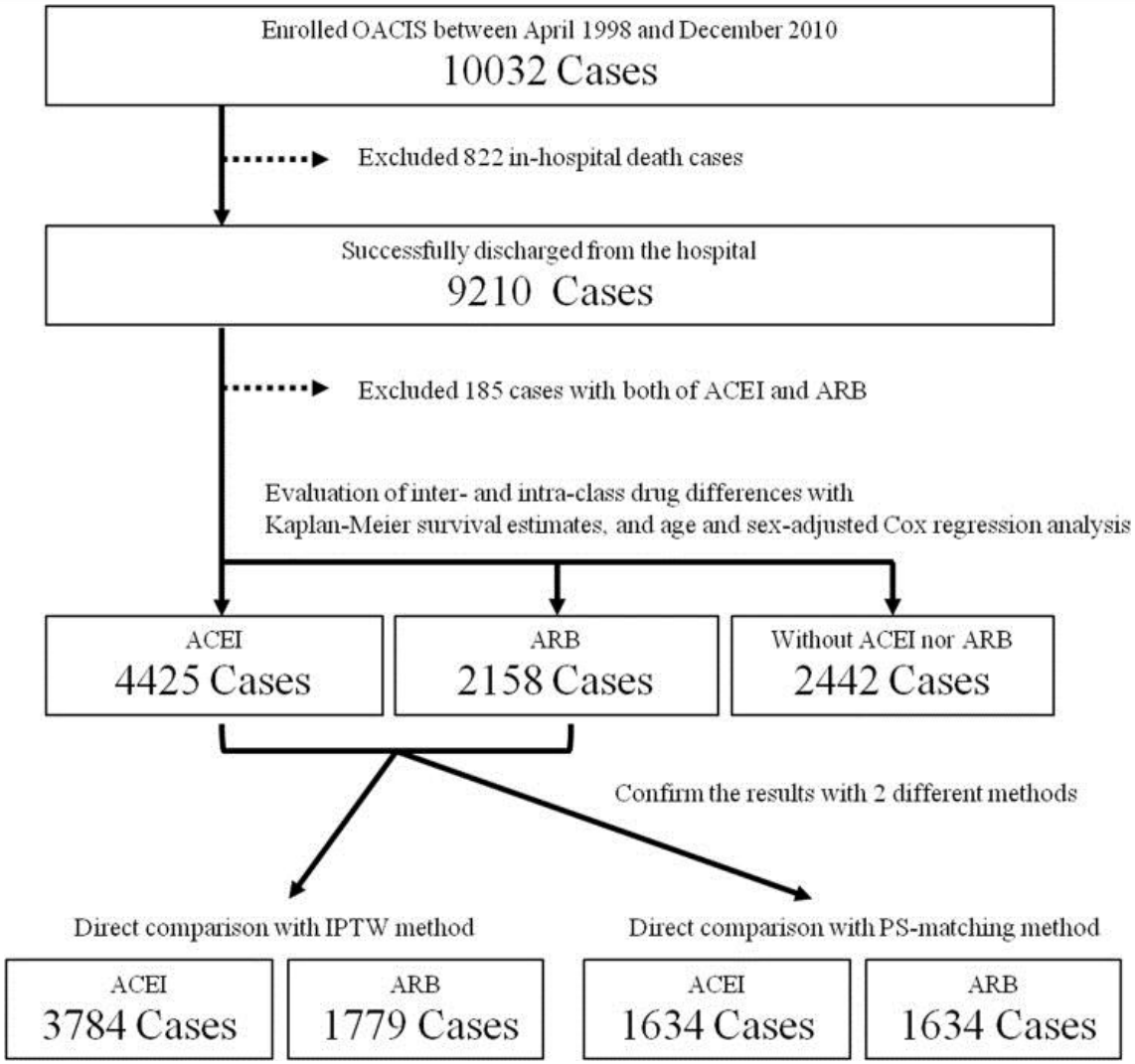
- Non-randomized nature of the registry data
- Underpowered study
  - The actual power was only around 50%.
- Lack of data on the specifics of the renin angiotensin system blocker, dose administered, and duration
- Adverse clinical events were not centrally adjudicated in our registry.
- A median follow-up of 12-months.

Summary

In STEMI patients with preserved LV systolic function who underwent primary PCI,

- The ARB group had a similar risk of cardiac death or MI compared with the ACE inhibitor group and a lower risk of cardiac death or MI compared with the no RAS blocker group.
- Furthermore, the association with favorable outcomes of ARB therapy in terms of cardiac death or MI was consistent across various subgroups.

Osaka Acute Coronary Insufficiency Study (OACIS)



Baseline characteristics

Parameter	No RASI (n = 2442)	ACEI (n = 4425)	ARB (n = 2158)	p-Value (Total)	p-Value (ACEI vs ARB)
Age (years)	67 (59–75)	65 (57–73)	67 (59–75)	<0.001	<0.001
Men	73.6%	77.9%	74.3%	<0.001	0.001
Body mass index (kg/m^2)	23.0 (21.0–25.2)	23.5 (21.5–25.7)	23.9 (21.6–26.0)	<0.001	0.001
ST-elevation myocardial infarction	82.3%	86.8%	83.7%	<0.001	<0.001
Diabetes mellitus	34.7%	32.6%	34.0%	0.19	0.27
Hypertension	49.4%	59.3%	70.3%	<0.001	<0.001
Dyslipidemia	40.6%	44.8%	46.5%	<0.001	0.19
Smoking	59.3%	66.0%	61.5%	<0.001	<0.001
Previous myocardial infarction	13.6%	11.9%	10.8%	0.02	0.18
KILLIP class				<0.001	0.01
1	79.5%	85.4%	84.2%		
2	9.1%	8.4%	7.4%		
3	4.1%	3.3%	4.4%		
4	7.3%	2.9%	4.0%		
Emergent coronary angiography	92.7%	95.3%	96.2%	<0.001	0.10
Target Lesion				<0.001	0.22
Left main	3.1%	0.9%	1.3%		
Left anterior descending artery	38.6%	47.9%	46.2%		
Right coronary artery	38.7%	34.9%	34.2%		
Left circumflex artery	16.3%	12.9%	14.8%		
Diagonal branch	3.0%	3.2%	3.4%		
Graft	0.4%	0.1%	0.1%		
Reperfusion therapy					
Percutaneous coronary intervention	80.4%	89.8%	93.2%	<0.001	<0.001
Thrombolysis	8.2%	7.1%	6.6%	0.12	0.49
Coronary artery bypass graft	6.6%	0.9%	1.4%	<0.001	0.07

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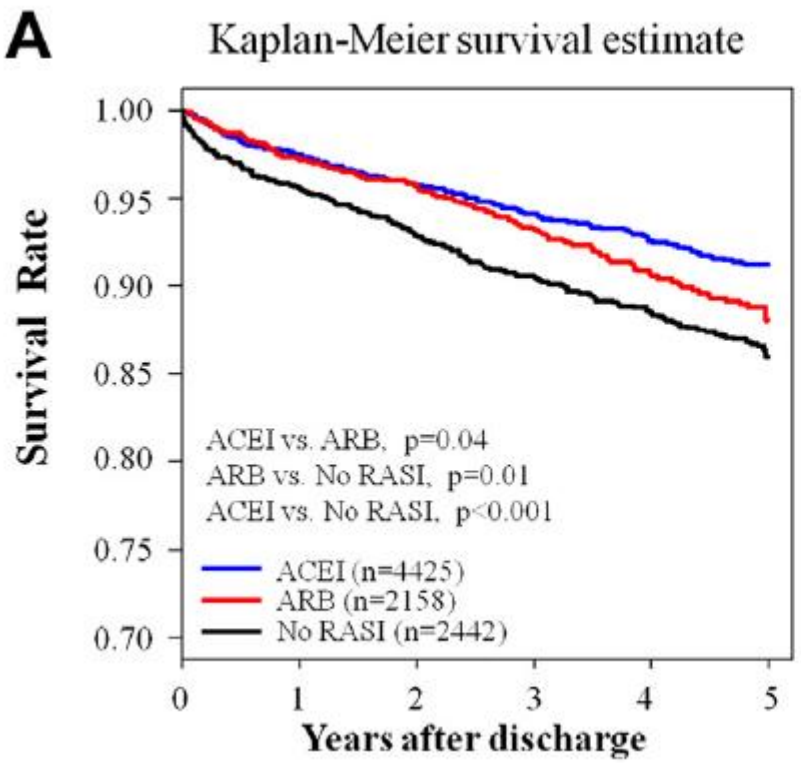
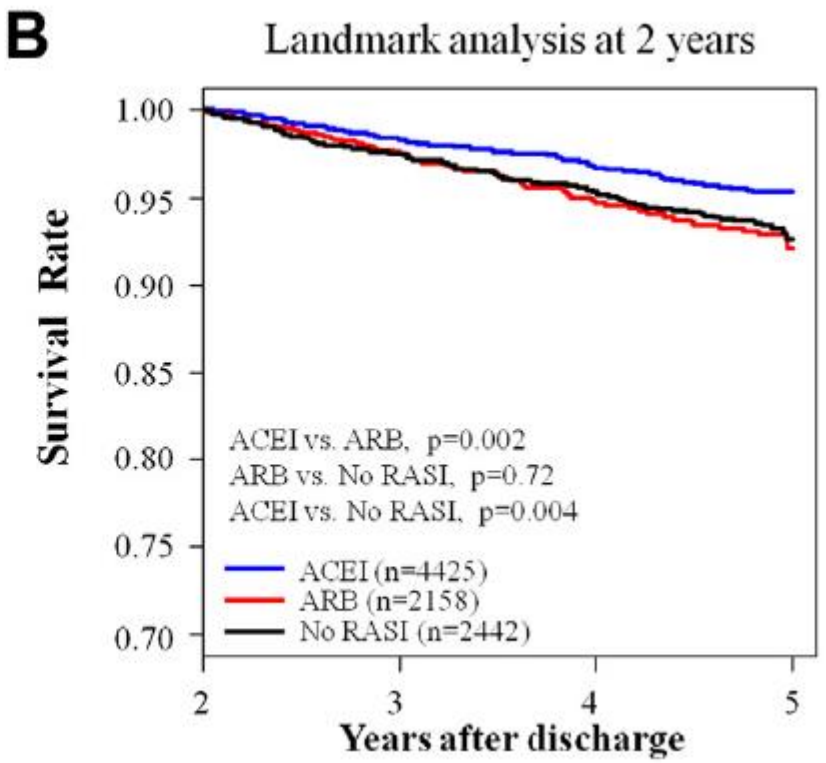
Comparison of 5-Year Survival





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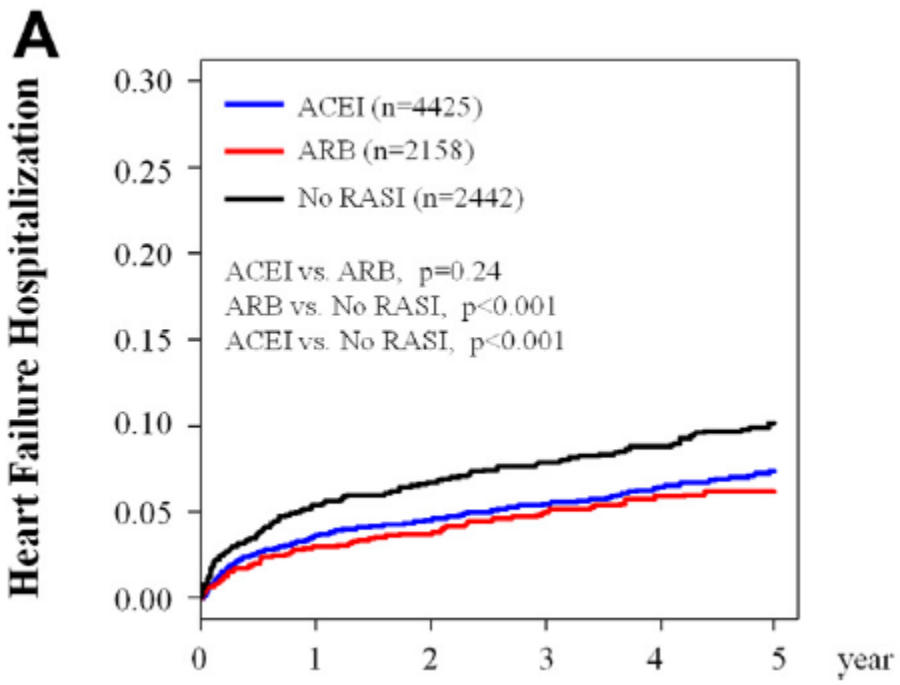
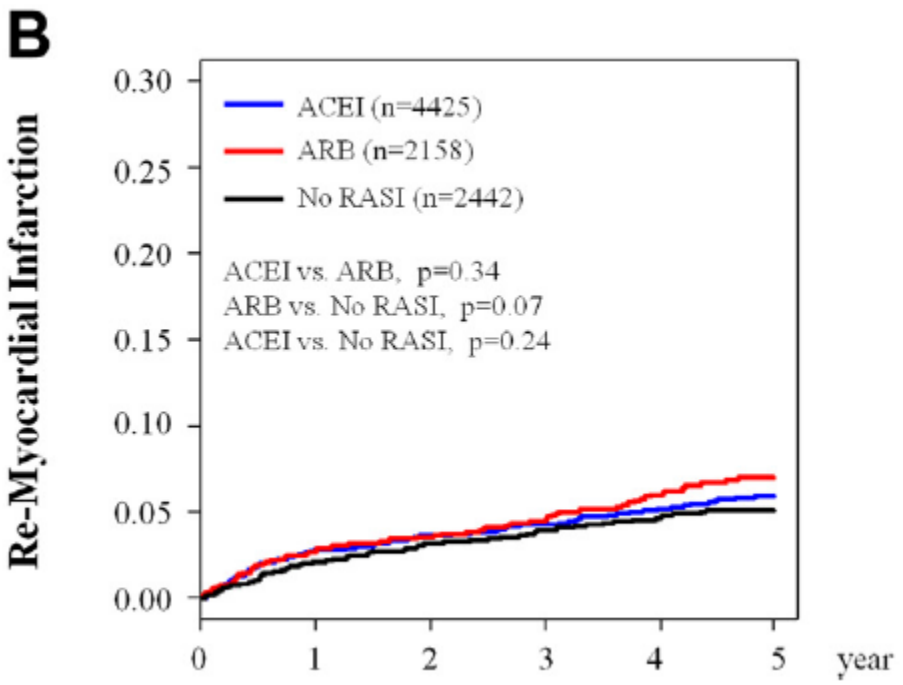
Heart failure and Re-MI





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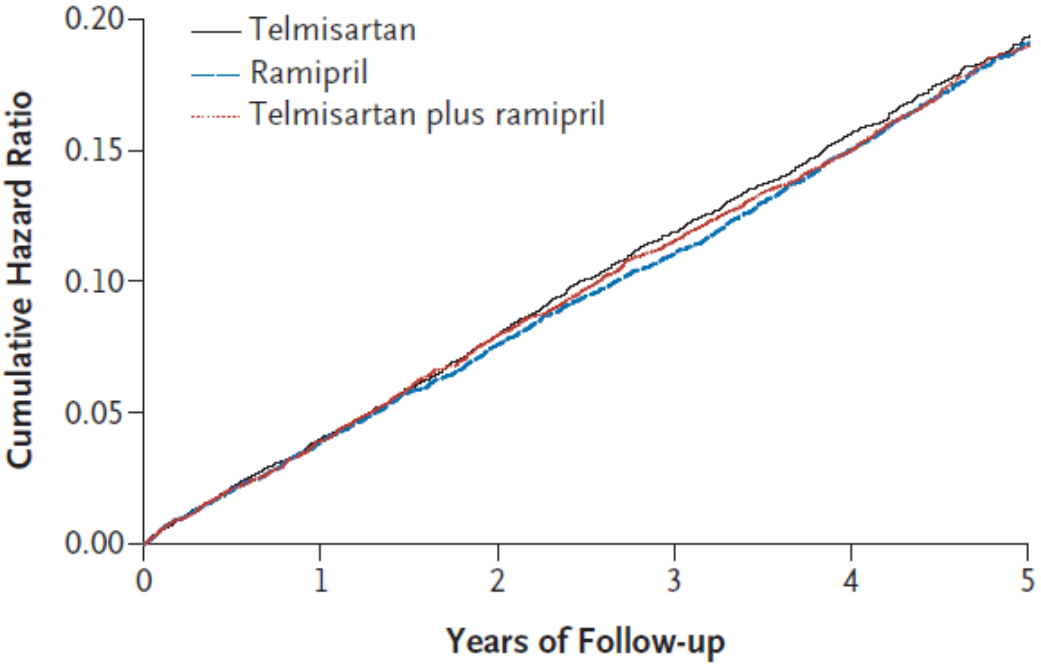
ARB vs. ACEi in high risk patients

ON TARGET trial

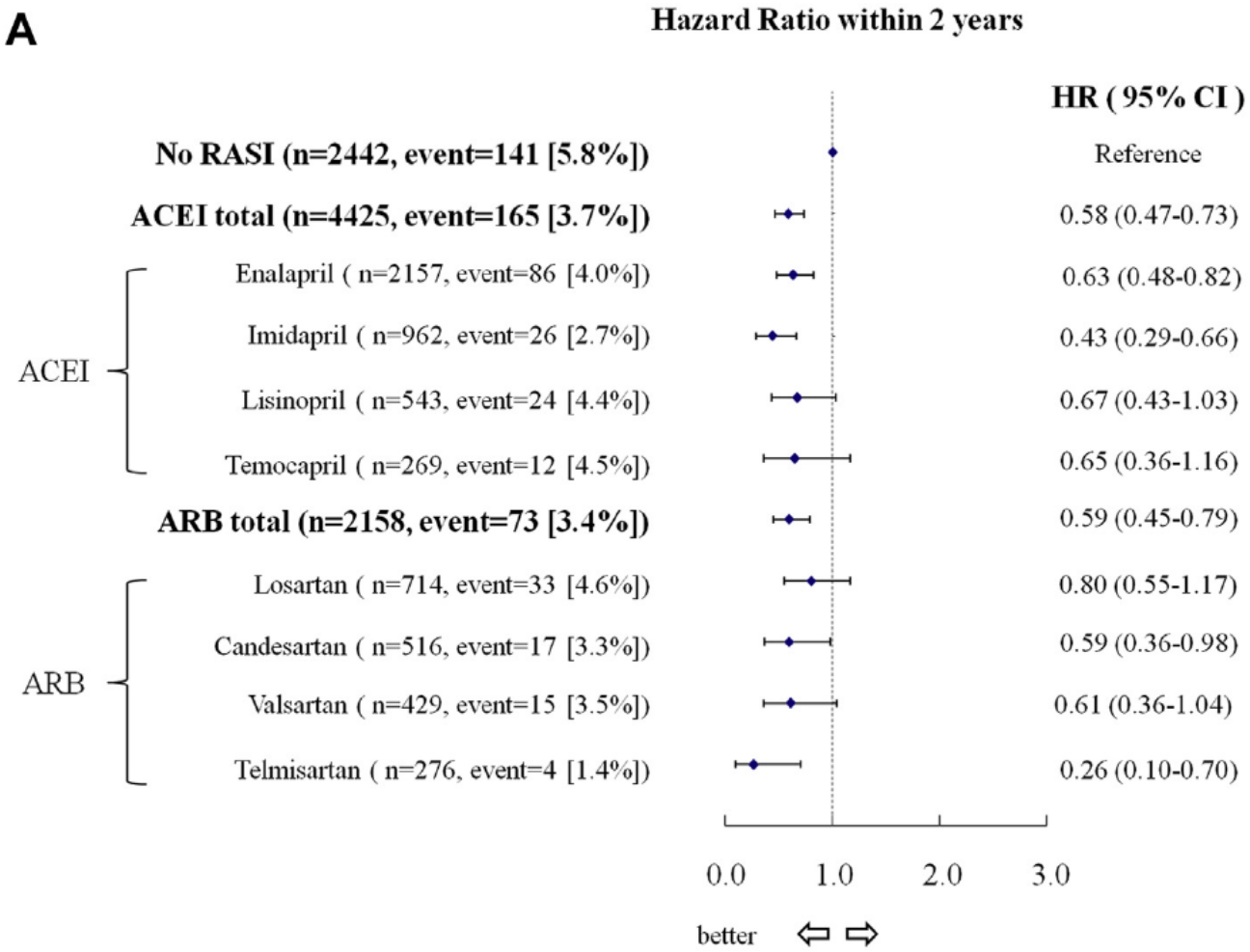
CV death, MI, stroke, or hospitalization for heart failure



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

N Engl J Med 2008;358:1547-59

Inter- and intra-class drug differences for mortality



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Conclusions

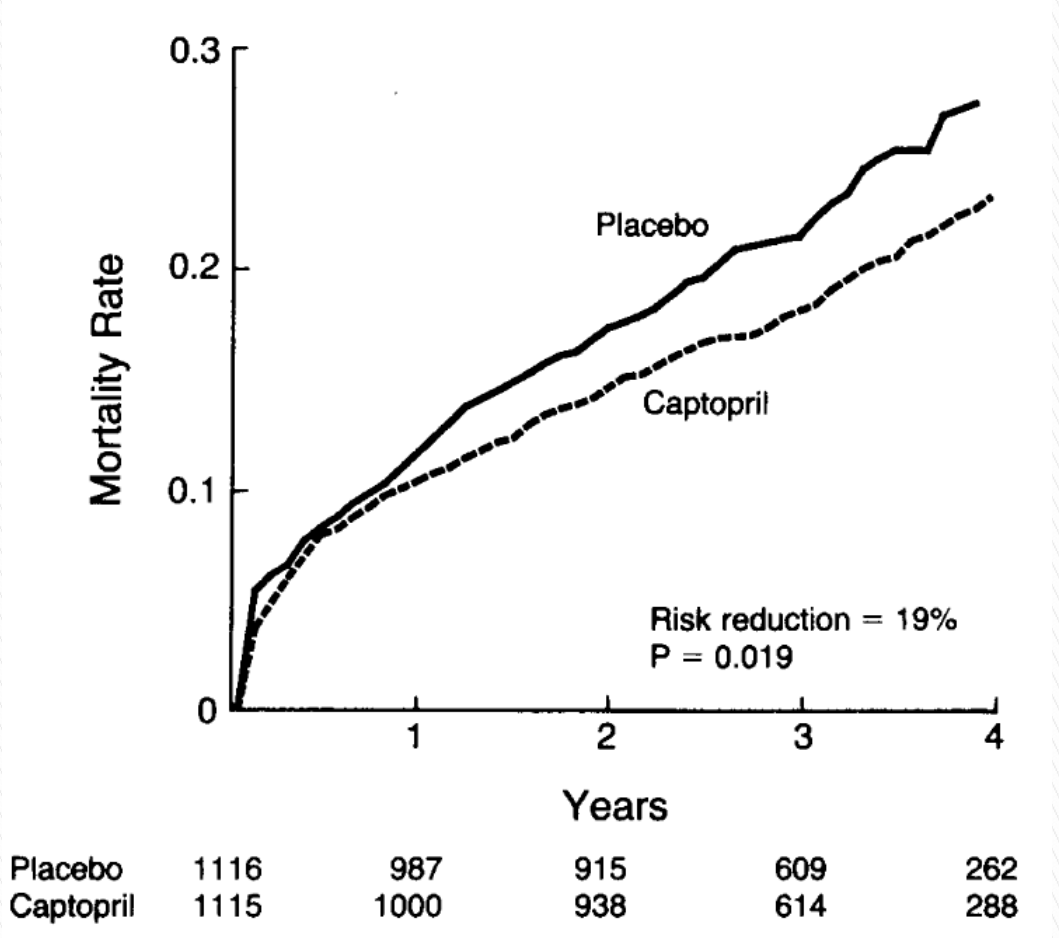
- An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction.
- Data from the Korean registry suggest that ARBs can be used an alternative to ACE inhibitors in STEMI patients with preserved LV systolic function.
- However, the role of ARB in AMI patients with preserved LV systolic function remains controversial.
  - Which ARB?
  - Long-term follow-up.
- A large randomized trial is needed.

감사합니다.
Thank you for your attention.

ACE inhibitors after STEMI

SAVE trial

- Patients with AMI
- LV ejection fraction <40%
- Captopril 50 mg tid



N Engl J Med. 1992;327:669-77.

Baseline characteristics

Thrombolytic therapy (%)	32	34
Cardiac catheterization (%)	54	57
PTCA (%)	17	17
Coronary-artery bypass surgery (%)	8	10
Infarct type and location (%)‡		
Anterolateral Q wave	54	56
Inferoposterior Q wave	17	18
Both	12	11
Non–Q wave	10	10
Other	7	5
Medication use within 24 hr of randomization (%)		
Antiarrhythmic drugs	11	14
Anticoagulant agents	28	28
Aspirin	59	59
Other antiplatelet agents	14	14
Beta-blockers	36	35
Calcium-channel blockers	42	42
Digitalis	27	25
Diuretics	35	35
Nitrates	53	50

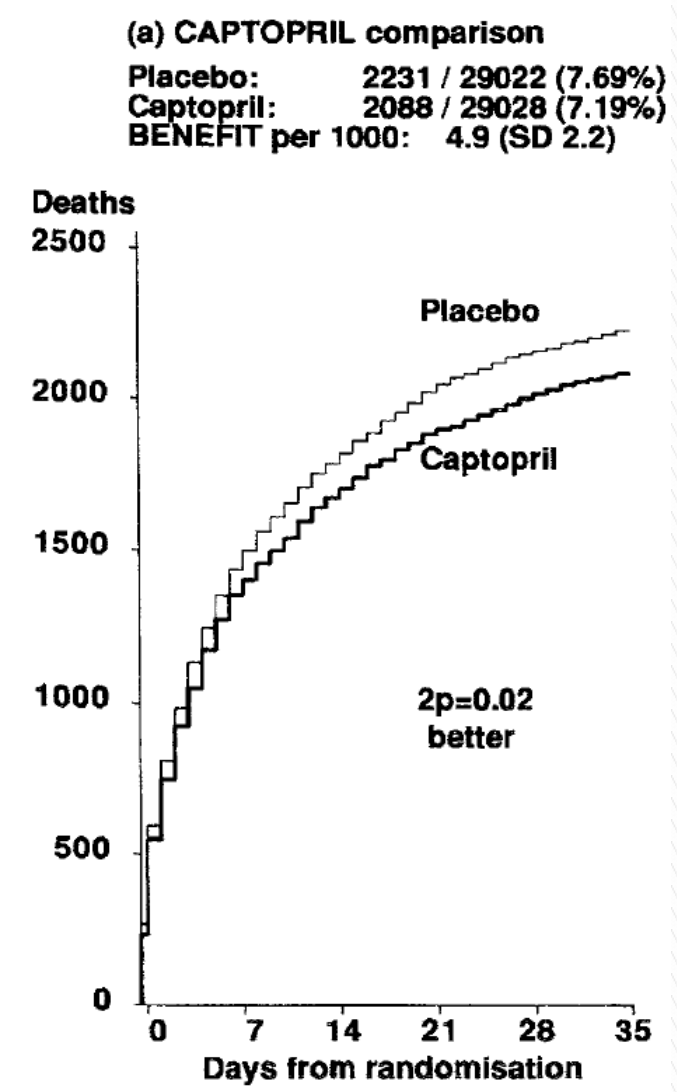
ACE inhibitors after STEMI

ISIS-4

- Patients with suspected AMI
- Captopril 50 mg bid

- STEMI 79%
- Fibrinolytic therapy 70%

- Larger benefit in patients with heart failure



Lancet. 1995;345:669-85.

VALIANT trial

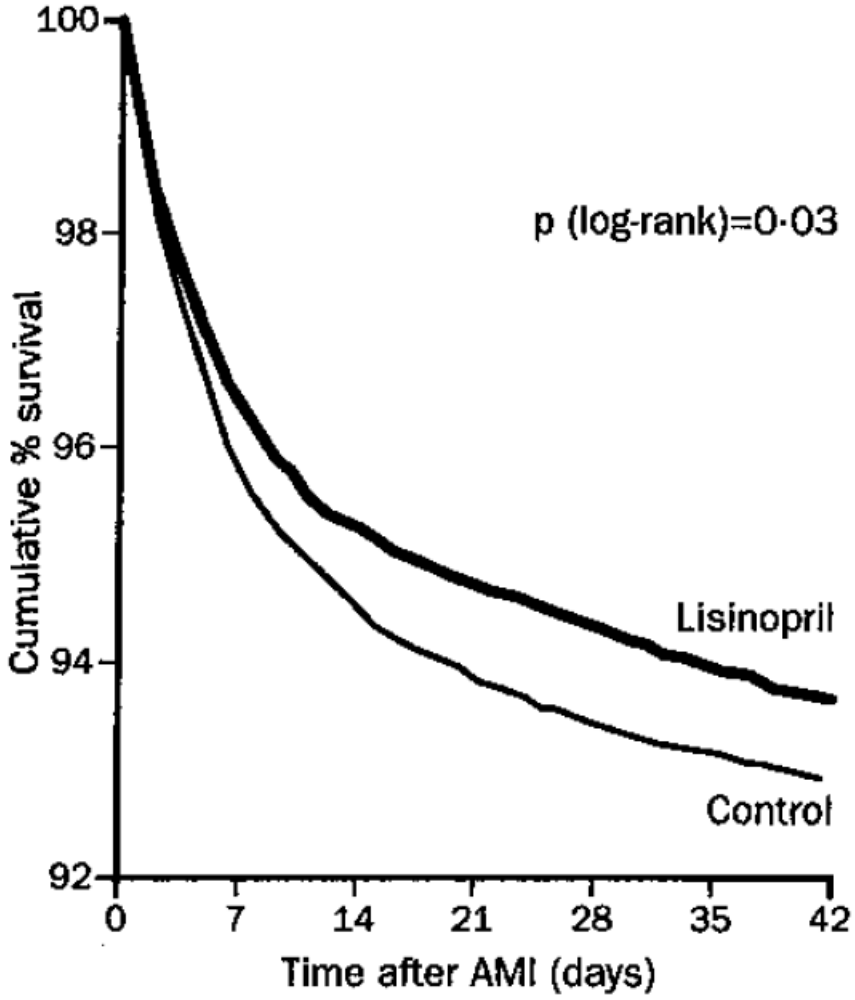
Site of qualifying myocardial infarction — no. (%)			
Anterior	2765 (58.7)	2831 (60.3)	2796 (59.3)
Inferior	1586 (34.1)	1601 (34.4)	1618 (34.7)
Type of qualifying myocardial infarction — no. (%)			
Q-wave	3116 (65.8)	3132 (66.4)	3195 (67.5)
Non–Q-wave	1512 (32.5)	1494 (32.2)	1452 (31.1)
Thrombolytic therapy — no. (%)	1741 (35.5)	1711 (35.0)	1718 (35.0)
Primary percutaneous coronary intervention — no. (%)	731 (14.9)	730 (14.9)	717 (14.6)
Other percutaneous coronary intervention after myocardial infarction but before randomization — no. (%)	1012 (20.6)	949 (19.4)	955 (19.5)
Medication — no. (%)‡			
ACE inhibitors	1936 (39.4)	1993 (40.8)	1888 (38.5)
Angiotensin-receptor blockers	54 (1.1)	53 (1.1)	67 (1.4)
Beta-blockers	3468 (70.6)	3439 (70.4)	3443 (70.1)
Aspirin	4481 (91.3)	4452 (91.1)	4485 (91.4)
Other antiplatelet agents	1232 (25.1)	1205 (24.7)	1210 (24.6)
Potassium-sparing diuretics	447 (9.1)	438 (9.0)	445 (9.1)
Other diuretics	2517 (51.3)	2459 (50.3)	2424 (49.4)
Hydroxymethylglutaryl coenzyme A reductase inhibitors	1658 (33.8)	1665 (34.1)	1691 (34.4)

ACE inhibitors in patients with AMI

GISSI-3

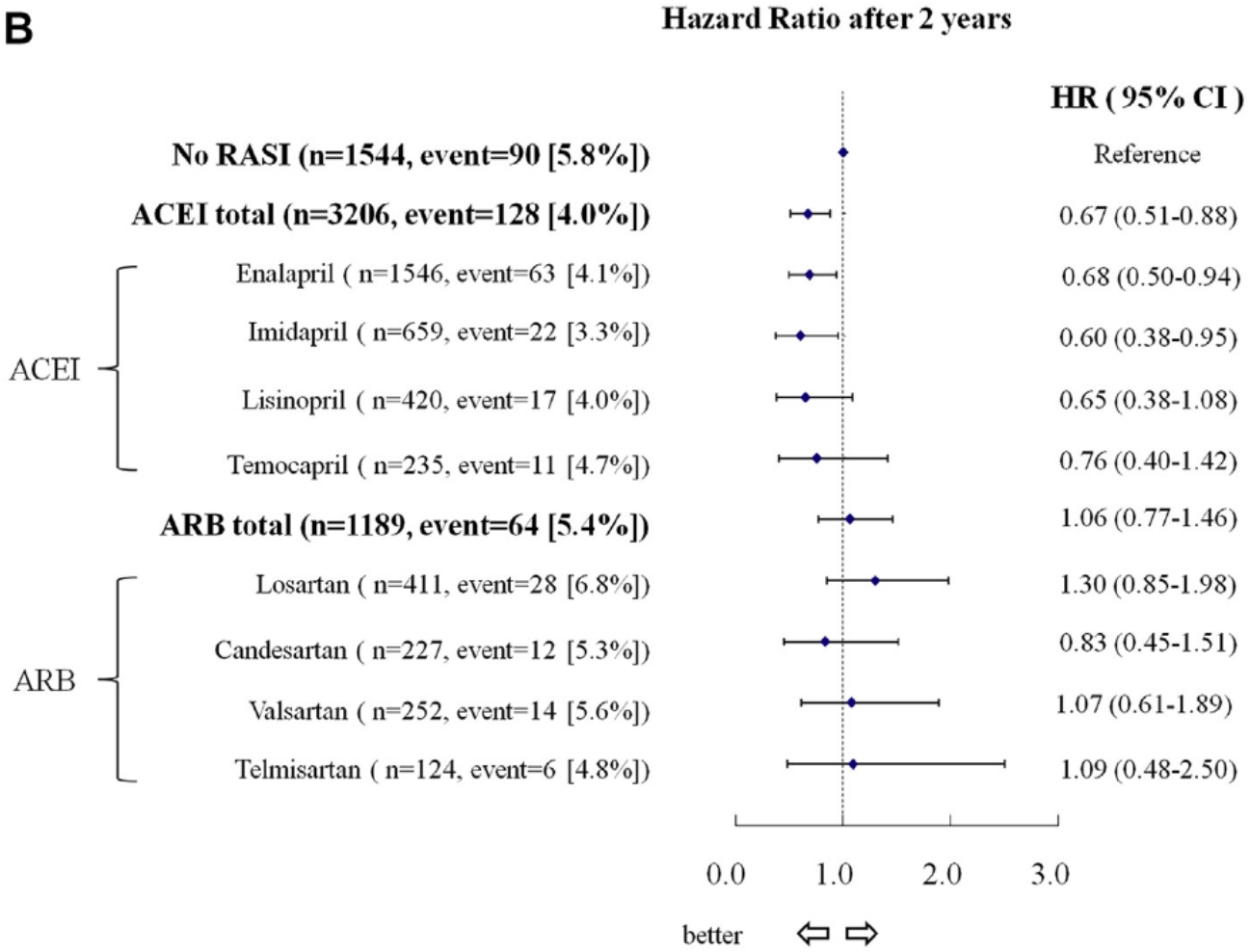
- Patients with AMI (n=19394)
- Lisinopril 50 mg bid

- Fibrinolytic therapy 70%



Lancet. 1994;343:1115-22.

Inter- and intra-class drug differences for mortality



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